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(54) Title: PERITONEAL DIALYSIS SOLUTION CONTAINING MODIFIED ICODEXTRINS (57) Abstract The present invention provides a peritoneal dialysis solution that contains heat stable osmotic agents such as D-glucitols, gluconic acids and alkylglycosides produced the reduction, oxidation or glycosylation of icodextrine respectively. As a result, osmotic agents that are stable under autoclaving or heat sterilization conditions are provided which reduces the amount of bioincompatible materials in the sterilized peritoneal dialysis solutions. Methods of preparing the D-glucitols, gluconic acids and alkylglycosides are disclosed.		

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S P E C I F I C A T I O NT I T L E

"PERITONEAL DIALYSIS SOLUTION CONTAINING
MODIFIED ICODEXTRINS"

B A C K G R O U N D O F T H E I N V E N T I O N

5 The present invention relates generally to
peritoneal dialysis and solutions for the same. More
specifically, the present invention relates to the use
of modified icodextrins in peritoneal dialysis
10 solutions as an osmotic agent and as an alternative to
the use of glucose as an osmotic agent. The present
invention also relates to methods of preparing
peritoneal dialysis solutions that are stable under
autoclaving conditions.

15 Dialysis provides a method for supplementing or
replacing renal function in certain patients.
Principally, hemodialysis and peritoneal dialysis are
the two methods that are currently utilized.

20 In hemodialysis, the patient's blood is passed
through an artificial kidney dialysis machine. A
membrane in the machine acts as an artificial kidney
for cleansing the blood. Because it is an
extracorporeal treatment that requires special
machinery, hemodialysis is fraught with certain
25 inherent disadvantages such as the availability of
dialysis machines and the possibility of infection and
contamination.

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To overcome the disadvantages associated with hemodialysis, peritoneal dialysis was developed. Peritoneal dialysis utilizes the patient's own peritoneum as a semi-permeable membrane. The
5 peritoneum is a membranous lining of the abdominopelvic walls of the body. The peritoneum is capable of acting as a natural semi-permeable membrane because of its large number of blood vessels and capillaries.

10 In operation, a peritoneal dialysis solution is introduced into the peritoneal cavity utilizing a catheter. After a sufficient period of time, an exchange of solutes between the dialysate and blood is achieved. Fluid removal is achieved by providing a
15 suitable osmotic gradient from the dialysate to the blood to permit water outflow from the blood. This allows the proper acid-base, electrolyte and fluid balance to be achieved in the blood. After an appropriate dwell period, the dialysis solution or
20 dialysate is drained from the body through a catheter.

Conventional peritoneal dialysis solutions contain glucose as an osmotic agent to maintain the osmotic pressure of the solution higher than the physiological osmotic pressure (about 285 mOsmol/kg).
25 Glucose is a preferred osmotic agent because it provides rapid ultrafiltration rates. However, certain disadvantages have become associated with the

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use of glucose.

For example, glucose is known to decompose to 5-hydroxymethyl-furfural (5-HMF) in an aqueous solution during autoclaving or steamed sterilization. Smith, et al. AM.J. Hosp. Pharm., 34:205-206 (1977). Because 5-HMF is considered to be harmful for the peritoneum (Henderson, et al., Blood Purif., 7:86-94 (1989)), it would be desirable to have a peritoneal dialysis solution with an osmotic agent as effective as glucose but which does not produce 5-HMF or other harmful decomposition products during autoclaving or sterilization. In short, a substitute osmotic agent for glucose is needed.

One family of compounds capable of serving as osmotic agents in peritoneal dialysis solutions is icodextrins, including maltodextrins. However, while these compounds are suitable for use as osmotic agents, they are also known to degrade during heat sterilization to aldonic acids and formaldehyde. Because the presence of formaldehyde in peritoneal dialysis solutions is inappropriate due to its poor biocompatibility, the use of icodextrins, including maltodextrins as a substitute for glucose as an osmotic agent is unsatisfactory.

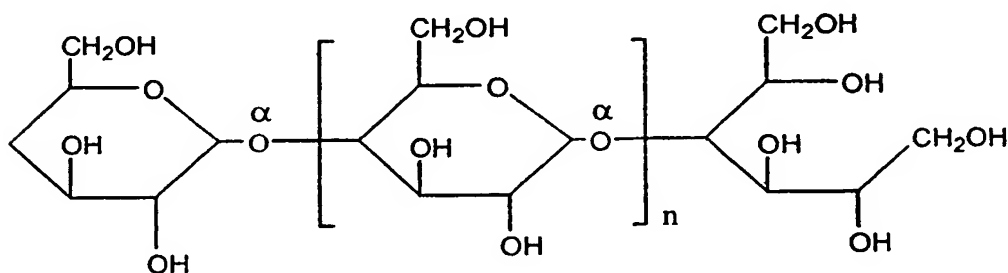
Accordingly, there is a need for an improved peritoneal dialysis solution which utilizes an osmotic agent other than glucose and which is stable under

autoclaving or steam sterilization conditions.

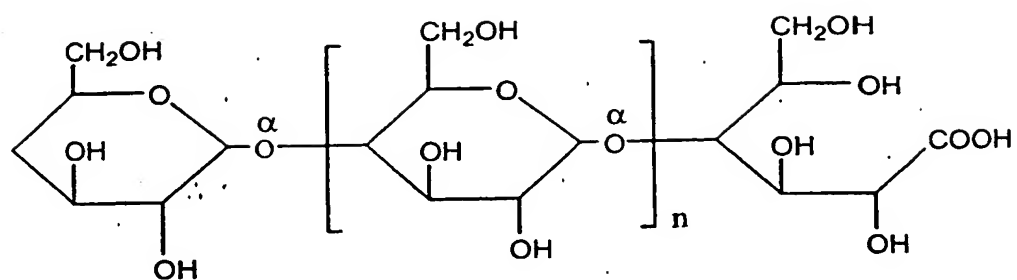
SUMMARY OF THE INVENTION

The present invention provides a solution to the
aforenoted need by providing a sterilized peritoneal
dialysis solution comprising a glucose polymer linked
predominately by α -1,4 bonds. The term "predominately"
is used because it is anticipated that within polymer
molecules, other bonds such as α -1,6 bonds will be
present as well, but in lesser amounts. Accordingly,
as used herein, the term "predominately" means at
least 85%. Thus, a glucose polymer linked
predominately by α -1,4 bonds includes at least 85%, by
number, α -1,4 bonds.

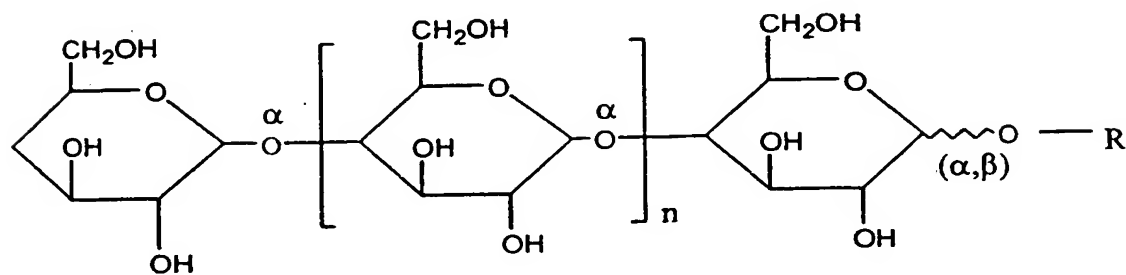
In an embodiment, the glucose polymer linked
predominately by α -1,4 bonds is selected from the
group consisting of D-glucitol having the formula



gluconic acid having the formula



15 and alkylglycoside having the formula



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wherein R is selected from the group consisting of CH_3 , CH_3CH_2 and $(\text{CH}_2\text{OH})_2\text{CH}$, $\text{CH}_2(\text{OH})\text{CH}(\text{OH})\text{CH}_2$, and $(\text{CH}_2\text{OH})(\text{CHOHCH}_2\text{OH})\text{CH}$.

5 In an embodiment, the glucose polymers, linked predominately by α -1,4 linkages, of the peritoneal dialysis solution may include up to 10% of other linkages including, but not limited to, α -1,6 linkages.

10 In an embodiment, the peritoneal dialysis solution of the present invention is substantially free of formaldehyde.

In an embodiment, the peritoneal dialysis solution of the present invention is substantially free of furfurals.

15 In an embodiment, starch utilized as the osmotic agent is substantially free of terminal aldehyde groups.

20 In an embodiment, the present invention provides a method of preparing a stabilized osmotic agent of a peritoneal dialysis solution comprising the steps of providing a solution of starch dissolved in water and adding NaBH_4 to the solution of partially hydrolyzed starch to reduce the starch.

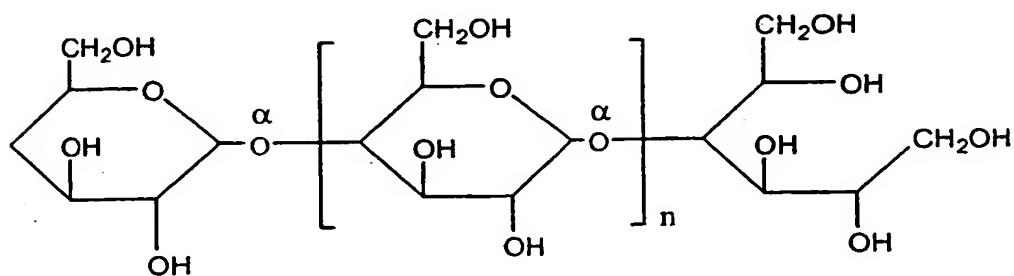
25 In an embodiment, the method of the present invention further comprises the step of purifying the reduced starch solution by passing the reduced starch solution through an anionic exchange resin.

In an embodiment, the dissolving and adding steps of the method of the present invention are carried out at room temperature.

In an embodiment, the method of the present invention further comprises the step of allowing the solution to scan for approximately 10 hours after the NaBH_4 is added to the starch solution to reduce the starch.

In an embodiment, the starch of the present invention is maltodextrin.

In an embodiment, the method of the present invention reduces maltodextrin to D-glucitol linked predominately by α -1,4 bonds and having the formula



In an embodiment, the present invention provides a method for preparing a stabilized osmotic agent of a peritoneal dialysis solution which comprises the steps of providing a solution of starch dissolved in water, providing a solution of NaOCl, and adding the NaOCl solution to the starch solution to oxidize the starch.

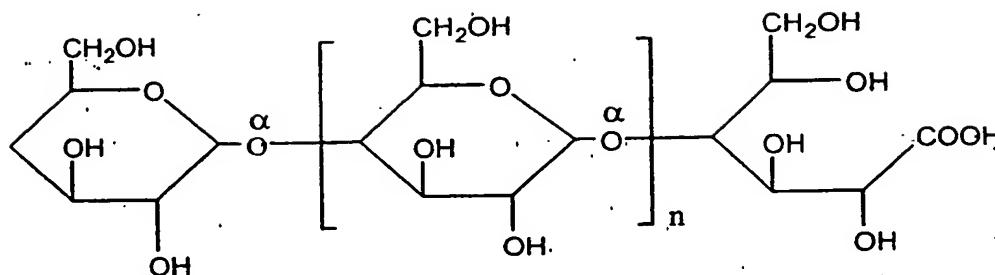
In an embodiment, the method of the present invention further comprises the step of purifying the oxidized starch solution by passing the oxidized starch solution through a gel permeation chromatograph.

In an embodiment, the oxidation of the starch is carried out at room temperature.

In an embodiment, the combined solutions are allowed to stand for approximately 2 hours.

In an embodiment, the starch is maltodextrin.

In an embodiment, the method of the present invention oxidizes the maltodextrin to a gluconic acid linked predominately by α -1,4 bonds and having the formula



In an embodiment, the maltodextrin can be oxidized electrochemically.

15 In an embodiment, the present invention provides a method of preparing a stabilized osmotic agent for a peritoneal dialysis solution which comprises the steps of dissolving the starch in an acid and an alcohol selected from the group consisting of methanol, butanol, glycerol or other alcohols.

20 In an embodiment, the method further comprises the step of stirring the starch, alcohol and acid for 2-16 hours.

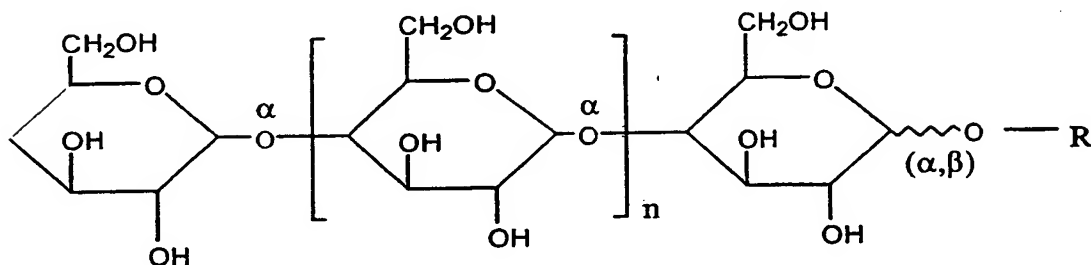
In an embodiment, the method further comprises the step of stirring the starch, alcohol and acid at a temperature of about 100°C.

25 In an embodiment, the starch is maltodextrin.

In an embodiment, the acid is hydrochloric acid or other acids such as sulfuric acid.

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In an embodiment, the method of the present invention hydrolyzes and alkylates the starch to an alkylglycoside linked predominately by α -1,4 bonds and having the formula



and wherein R is selected from the group consisting of CH_3 , CH_3CH_2 and $(\text{CH}_2\text{OH})_2\text{CH}$. When hydrolysis is performed on starch pre-treated with periodate, R is the remnant of a glycol-split glucose unit.

It is therefore an advantage of the present invention to provide an improved peritoneal dialysis solution which is stable under autoclaving and steam sterilization conditions.

Another advantage of the present invention is that it provides an improved osmotic agent as an alternative to glucose.

Yet another advantage of the present invention is that it provides improved methods of preparing peritoneal dialysis solutions.

5 Yet another advantage of the present invention is that it provides improved osmotic agents for peritoneal dialysis solutions which are stable under autoclaving or steam sterilization conditions.

10 Additional features and advantages of the present invention are described in, and will be apparent from, the detailed description of the presently preferred embodiments and upon reference to the accompanying figures.

BRIEF DESCRIPTION OF THE FIGURES

15 Figure 1 is a graphical illustration of the ^{13}C NMR spectrum of an osmotic agent prepared by glycosylation in accordance with the present invention; and

20 Figure 2 is a graphical illustration of the ^{13}C NMR spectrum of an osmotic agent prepared by glycosylation in accordance with the present invention.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

25 The present invention provides a peritoneal dialysis solution with osmotic agents that are stable under autoclaving and steam sterilization conditions. The stable osmotic agents of the present invention may

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be prepared by reduction, oxidation or glycosylation. When an icodextrin having reducing-end units are employed, such as maltodextrin, the reduction, oxidation or glycosylation procedures of the present invention transform the icodextrin to corresponding D-glucitols, gluconic acids and alkyglycosides respectively.

Example 1

A reduced icodextrin was prepared by starting with 15 grams of maltodextrin dissolved in 20 ml of water. One gram of NaBH_4 was added to the solution at room temperature and the solution was allowed to stand for 10 hours. The solution was then purified by passing it through an anionic exchange resin.

Three different maltodextrin starting materials were utilized. A low molecular weight (LMW) having a 3% degree of polymerization (DP) was utilized that contained 1% glucose, 37% maltose, 20% maltotetraose and 42% high molecular weight oligosaccharides.

Second, a high molecular weight maltodextrin (HMW1) having a 14% degree of polymerization was utilized and contained 1% glucose, 2% maltose, 4% maltotetraose and 94% high molecular weight oligosaccharides. Third, a second high molecular weight maltodextrin (HMW2) with a 9% degree of polymerization containing 1% glucose, 3% maltose, 7% maltotetraose and 90% high molecular weight oligosaccharides was utilized. The products

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and starting materials were analyzed using ^{13}C NMR spectroscopy. The signals associated with the reducing end units of the starting materials completely disappeared in the spectra of the products. Some depolymerization was observed.

The products were tested for stability under sterilization conditions at neutral pH. A significant reduction of absorbance variation at 284 nm (Δ Abs) after sterilization is observed for the reduced compounds. The reduced compounds from Example 1 are listed as HMW1 red, HMW2 red and LMW red in Table 1.

Example 2

Utilizing the three different samples of maltodextrins discussed above with respect to Example 1, oxidation reactions were carried out on each sample by dissolving 15 grams of maltodextrin in 30 ml of water and combining the starch solution with an effective amount of NaOCl in 70 ml of a solution containing sodium hydroxide and having a pH of 8 ± 0.5 at a temperature of 43°C . The combined solutions were allowed to stand for approximately 2 hours and the product solution was purified by gel permeation chromatography. Again, the products were analyzed using ^{13}C NMR spectroscopy and were tested for stability under sterilization conditions as illustrated in Table 1. While the oxidation products, HMW1 ox HMW2 ox and LMW ox show contrasting results,

this is attributed to the high molecular weight oxidized products not being completely purified.

5 Table 1 - Absorbance (284 nm) variation after sterilization (121°C 45 min) of 5% Icodextrin and modified Icodextrin solutions

CODE	Number of experiments	Δ Abs (pH 6.5-7.5)	Δ Abs (pH 5.5)
HMW1	6	0.65 \pm 0.30	0.59 \pm 0.35
HMW1 red	6	0.31 \pm 0.10	0.20 \pm 0.07
HMW1 ox	2	1.83 \pm 0.21	1.78 \pm 0.13
HMW2	8	1.21 \pm 0.71	0.62 \pm 0.71
HMW2 red	7	0.13 \pm 0.09	0.09 \pm 0.06
HMW2 ox	4	0.76 \pm 0.31	0.79 \pm 0.19
LMW	8	1.96 \pm 0.87	1.33 \pm 0.86
LMW red	8	0.18 \pm 0.11	0.17 \pm 0.07
LMW ox	3	0.01 \pm 0.01	0.02 \pm 0.01
Reference compounds			
Glucose	4	2.54 \pm 0.78	2.36 \pm 0.96
*Glucose	2	0.98	
*D(+)-Gluconolactone	1	0.01	

*Glucose and D(+)-Gluconolactone solutions are 2.5% at pH 7

Δ Abs = difference between absorbance after and before sterilization

Example 3

In a third method of preparing stable osmotic agents in accordance with the present invention, icodextrin were glycosylated. The glycosylation reactions were performed using starch as the starting material and alcohol as the alkylating agent. Butanol and glycerol were chosen because of their

biocompatibility. The molecular weight of the reaction products depends upon the temperature, time and acid concentration used.

The hydrolysis with methanol and butanol were performed by stirring a suspension of 200 mg of starch in 540 mg of alcohol containing 60 mg of acid at a temperature of about 100°C for approximately 2 hours. The ^{13}C NMR spectrum of the two products obtained from this reaction with methanol and butanol respectively are shown in Figures 1 and 2. Table 2 presents the degree of polymerization (DP) and the percentage of non-substituted reducing ends as a function of the reaction conditions. This data was obtained from the ratio between the appropriate NMR signals (^1H NMR for DP values and ^{13}C NMR for the percentage of nonsubstituted reducing ends).

Table 2 - Glycosylation reaction with MeOH and ButOH

Sample No.	Alcohol	Acid M/t	D.P.	% non substituted glucose
1	MeOH	H_2SO_4	4.1	8.7
2	MeOH	HCl	5.2	11.2
3	ButOH	H_2SO_4	1.3	41.6
4	ButOH	HCl	1.4	13.0

Example 4

In the case of alcoholysis with glycerol, the reactions were performed using 1 gram of undried

starch (humidity 9%) and 2.7 grams of glycerol and stirring the mixture at 100°C with different amounts of hydrochloric acid for different time periods.

Glycerol excess was eliminated by evaporation under reduced pressure and further purification was performed by gel filtration. The results are shown in Table 3.

Table 3 - Glycosylation reaction with glycerol
(Standard reaction conditions: undried starch 1g, glycerol 2.7g)

Compound	Temperature °C	Time h	HCl Mol/L	Yield %	DP	% non substituted red. end
5*	80	2	1.27	n.d.	8.5	9.8
6**	100	2	1.27	96	1.4	4.8
7	100	2	1.27	n.d.	4.7	0
8	100	2	2.54	77.1	1.6	10.4
9	100	2	5.08	87.7	1.7	28.2
10	100	2	5.08	81.9	2.0	26.8
11	100	2	5.08	79.3	2.1	25.7
12	100	4	1.27	98	1.5	6.4
13	100	4	5.08	95.8	1.2	19.2
14	100	4	5.08	85.7	1.2	20.9
15	100	16	1.27	99.3	1.4	0
16***	100	16	1.27	93.1	1.2	0
17	100	16	5.08	78.9	1.0	13.4
18	100	16	5.08	79.6	1.0	0
19	100	24	5.08	82.1	1.0	4.6
20	60	16	1.27	n.d.	1.35	17.1
21	60	16	1.27	n.d.	1.10	23.9
22	80	16	0.32	88.7	1.11	13.9

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23	80	16	0.32	79.4	1.10	11.3
24	80	16	0.32	89.1	1.15	10.6
25	80	16	0.64	94.2	1.04	17.9
26	80	16	0.64	n.d.	1.03	21.7
27	80	16	0.64	n.d.	1.10	9.7
28	80	16	1.27	n.d.	1.03	11.4
29	80	16	1.27	99.8	1.01	8.6
30	80	16	1.27	n.d.	1.01	4.9

* Reaction conditions: starch 200 mg, glycerol 540 mg
 ** Reaction conditions: starch 600 mg, glycerol 1.62 g
 *** Reaction conditions: dry starch 1 g, glycerol 2.7 g

The ^{13}C NMR spectrum of the completely depolymerized product and of one with a degree of polymerization of 4.7 are shown in Figure 2. It is possible to observe the glycosidic anomeric signals α (100.9 ppm) and β (105.1 ppm), the CH_2 signals of both substituted (α = 71.3 ppm, β = 73 ppm) and non substituted (65.3 ppm) primary hydroxyl groups of glycerol, the CH signals (α = 81.5 ppm, β = 83 ppm) of secondary substituted hydroxyl group of glycerol.

The stability of one product shown in Table 3 was tested for stability under sterilization conditions and the observed variation at 284 nm is compared with that of glucose and methyl glycoside.

Table 4 - Absorbance (284 nm) variation after sterilization (121°C 45 min) of glycerol derivative and methyl glycoside

Sample	% (w/v)	number of experiments	Δ Abs neutra (pH 6.5-7.5)	Δ Abs acid (pH 5.5)
No. 6	5	-	0.46 ± 0.32	0.35 ± 0.15
glucose	5	3	2.43 ± 0.9	n.d.
Methyl glycoside	2.5	1	0.01	n.d.
glucose	2.5	1	0.07	n.d.

In an in vitro test predictive of the dialytic efficiency of the osmotic agents described above, small dialysis bags with Spectra Pore membrane with a cut-off 500 Dalton (diameter 15 mm, 15 cm high) were filled with 3 ml of water solutions at different concentrations (2.5, 5.0% w/v of the samples). The bags were immersed in 200 ml of distilled water and 37°C while stirring the extra dialysis solution. At given times (0, 1, 2, 3, 4, 5, 6 hours), the increase in the volume inside the dialysis bag was evaluated by weight and expressed as a percentage increase compared to the starting volume ($\Delta w\%$). The mean results are shown in Table 5 and are compared with the results for glucose and glucose-1-phosphate.

Table 5 - Volume increase in vitro dialysis test of modified icodextrins

Samples	Moles/L	N of experiments	$\Delta w\%$ 1h	$\Delta w\%$ 2h	$\Delta w\%$ 3h	$\Delta w\%$ 4h	$\Delta w\%$ 5h	$\Delta w\%$ 6h
LMW red	0.071	5	29.9	43.0	53.8	66.2	76.7	88.3
LMW ox	n.d.	5	20.2	29.2	39.3	46.0	56.4	63.4
HMW1 red	0.016	3	50.8	67.4	74.7	81.5	85.7	91.2
HMW1 ox	n.d.	3	22.8	43.3	60.2	77.0	89.6	104.2
HMW2 red	0.049	3	6.7	10.0	15.7	19.2	21.2	26.3
HMW2 ox	n.d.	4	32.2	52.9	69.7	84.2	96.0	106.4
No. 6 (5%)	0.215	1	33.2	68.2	98.1	119.5	140.5	159.8
α -methyl-gluc. (5%)	0.257	1	30.9	60.7	86.5	107.9	123.2	142.0
β -methyl-gluc. (5%)	0.257	1	45	76.1	103.0	129.7	151.7	174.9
No. 6 (2.5%)	0.108	2	22.9	34.4	50.0	63.0	77.2	87.7
α -methyl-gluc. (2.5%)	0.128	3	21.8	39.2	55.4	67.64	79.5	92.1
β -methyl-gluc. (2.5%)	0.128	3	34.0	50.3	63.7	67.6	77.7	86.5
glucose (2.5%)	0.138	3	15.3	34.2	43.4	57.3	74.2	90.9
gluc.-1-phos. (2.5%)	0.069	3	35.8	53.6	76.3	95.9	120.1	144.1

Accordingly, the present invention provides a number of heat stable osmotic agents that provide a suitable substitute for glucose, improved peritoneal dialysis solutions containing stable osmotic agents as well as a variety of methods of producing improved peritoneal dialysis solutions.

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications may be made without departing from the spirit and scope of the

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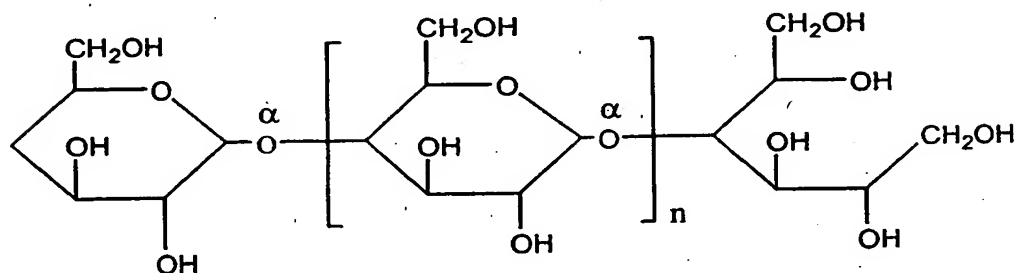
present invention and without diminishing its attendant advantages. It is, therefore, intended that such changes and modifications be covered by the appended claims.

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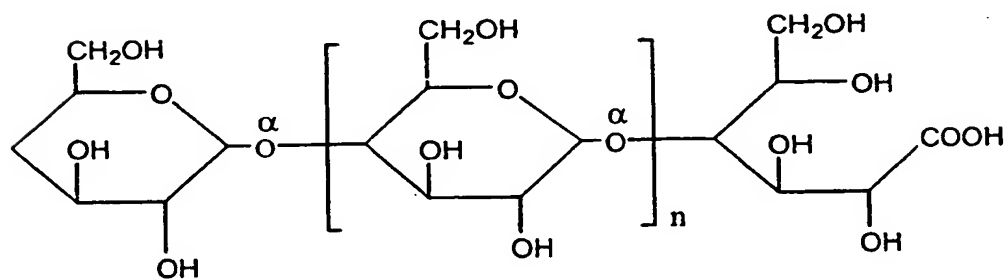
WHAT IS CLAIMED IS:

1. A sterilized peritoneal dialysis solution comprising:

a starch comprising a glucose polymer linked by bonds and selected from the group consisting of D-glucitol having the formula:

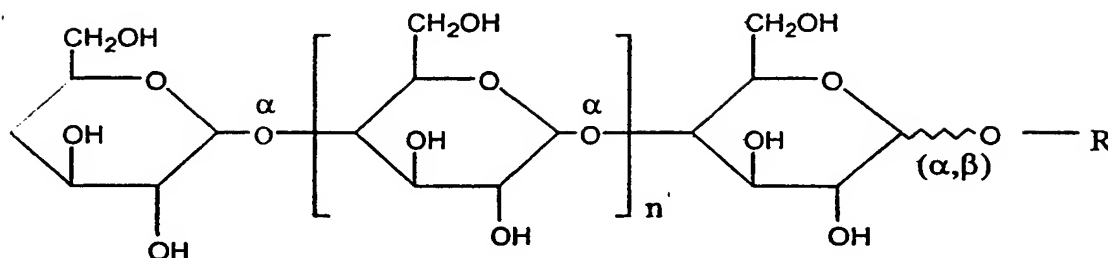


gluconic acid having the formula



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and alkylglycoside having the formula



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wherein R is selected from the group consisting of CH_3 , CH_3CH_2 , $(\text{CH}_2\text{OH})_2\text{CH}$, $\text{CH}_2(\text{OH})\text{CH}(\text{OH})\text{CH}_2$, and $[\text{CH}_2(\text{OH})\text{CH}(\text{OH})\text{CH}_2(\text{OH})]\text{CH}$ and wherein the bonds linking the polymer include at least 85%, by number, α -1,4 bonds.

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15

2. The peritoneal dialysis solution of claim 1 wherein the solution is absent of formaldehyde.

3. The peritoneal dialysis solution of claim 1 wherein the solution is absent of furfurals.

20

4. The peritoneal dialysis solution of claim 1 wherein the partially hydrolyzed starch is absent of

terminal aldehyde groups.

5 5. A method of preparing a stabilized osmotic agent for a peritoneal dialysis solution comprising the following steps:

 providing a solution of starch dissolved in water;

 adding NaBH_4 to the starch solution to reduce the starch.

10

 6. The method of claim 5 further comprising the step of

 purifying the reduced starch solution by passing the reduced starch solution through an anionic
15 exchange resin.

 7. The method of claim 5 wherein the dissolving and adding steps are carried out at room temperature.

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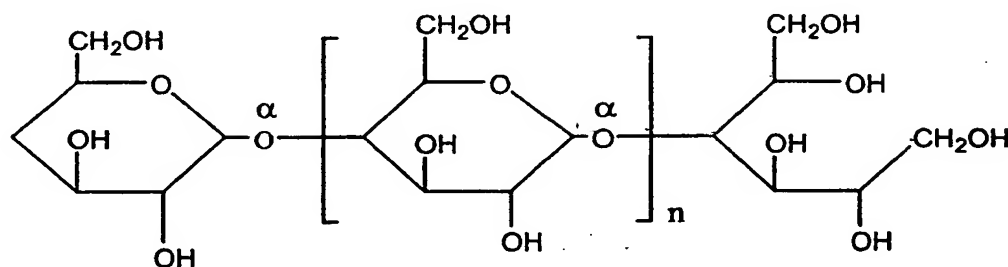
 8. The method of claim 6 further comprising the following step after the adding step and prior to the purifying step:

 allowing the solution to stand for about 10 hours.

25

 9. The method of claim 5 wherein the starch is maltodextrin.

10. The method of claim 5 wherein the starch is reduced to an icodextrin linked predominately by α -1,4 bonds and having the formula:



11. A method of preparing a stabilized osmotic agent for a peritoneal dialysis solution comprising the following steps:

providing a solution of starch dissolved in water;

providing a solution of NaOCl;

adding the NaOCl solution to the starch solution to oxidize the starch.

12. The method of claim 11 further comprising the step of

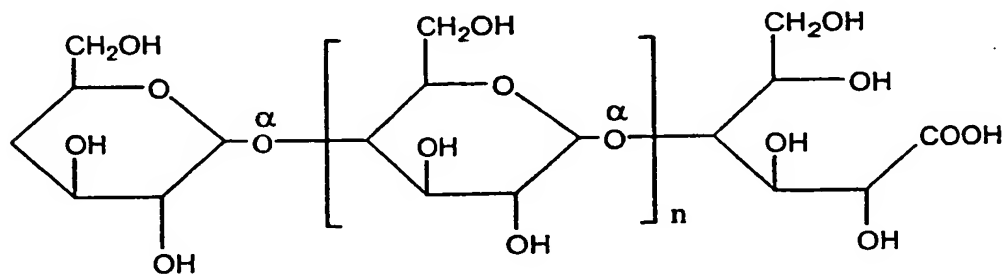
purifying the oxidized starch solution by passing the oxidized starch solution through a gel permeation chromatograph.

5 13. The method of claim 11 wherein the adding step is carried out at room temperature.

14. The method of claim 12 further comprising the following step after the adding step and prior to
10 the purifying step:
allowing the solution to stand for about 2 hours.

15 15. The method of claim 11 wherein the starch is maltodextrin.

16. The method of claim 11 wherein the starch is oxidized to an icodextrin linked predominately by α -1,4 bonds and having the formula:



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17. A method of preparing a stabilized osmotic agent for a peritoneal dialysis solution comprising the following steps:

5 dissolving starch in an acid and an alcohol selected from the group consisting of methanol, butanol and glycerol.

18. The method of claim 17 further comprising the step of

10 stirring the starch, alcohol and acid for about 2 hours.

19. The method of claim 17 wherein the stirring step is carried out at a temperature of about 100°C.

15

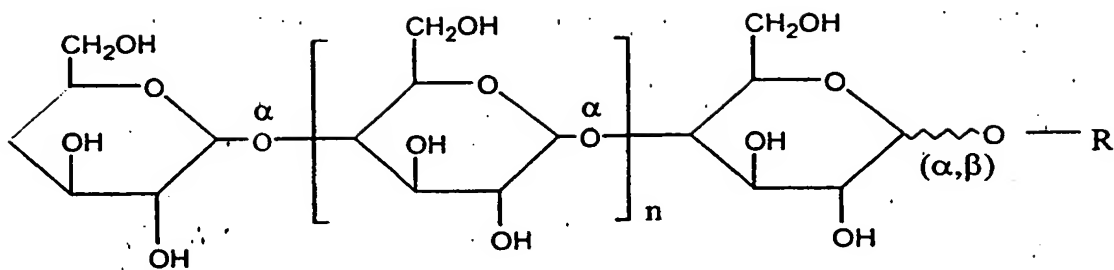
20. The method of claim 17 wherein the starch is maltodextrin.

21. The method of claim 17 wherein the acid is HCl.

20

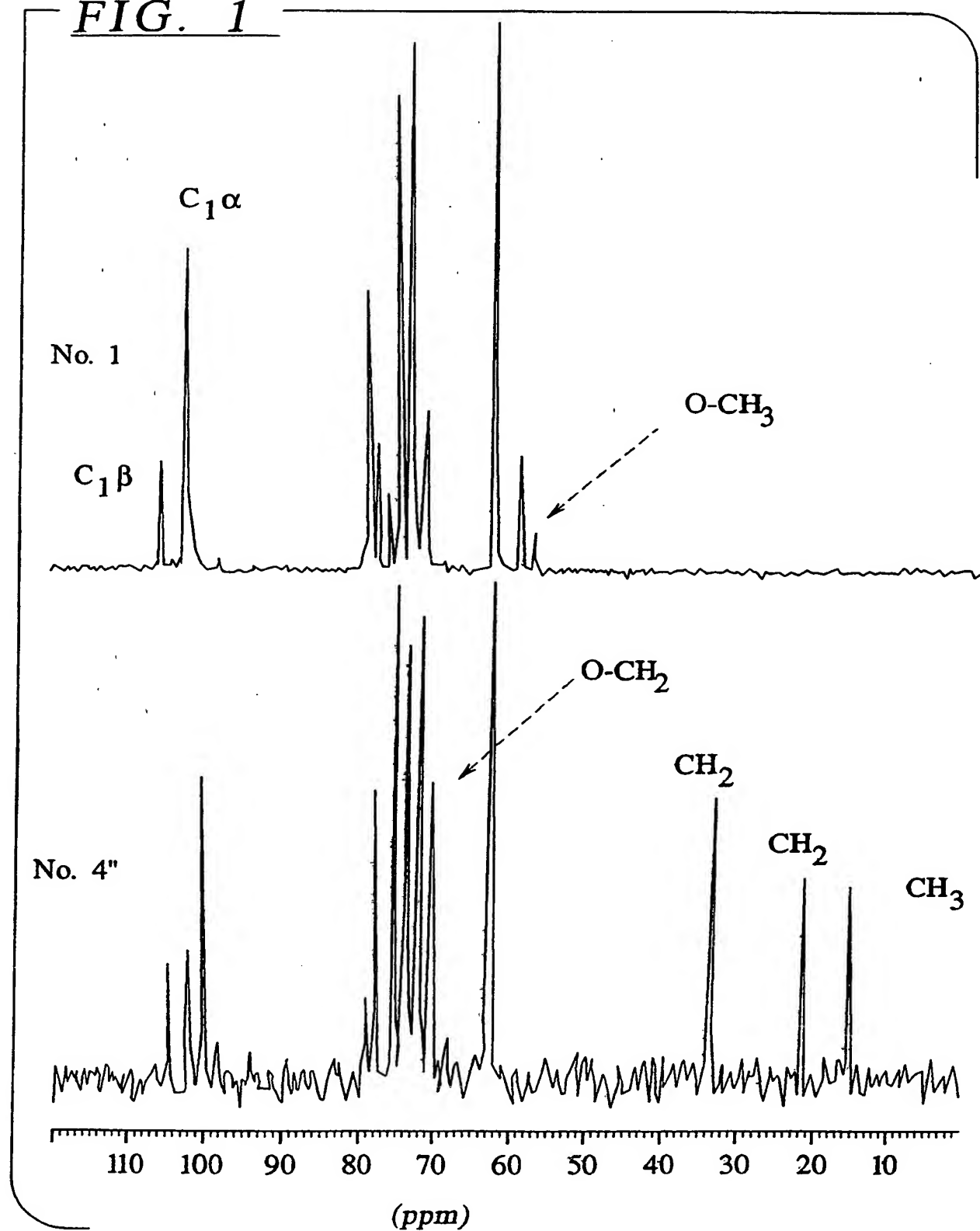
22. The method of claim 17 wherein the starch is glycosylated to an icodextrin linked predominately by α -1,4 bonds and having the formula:

25

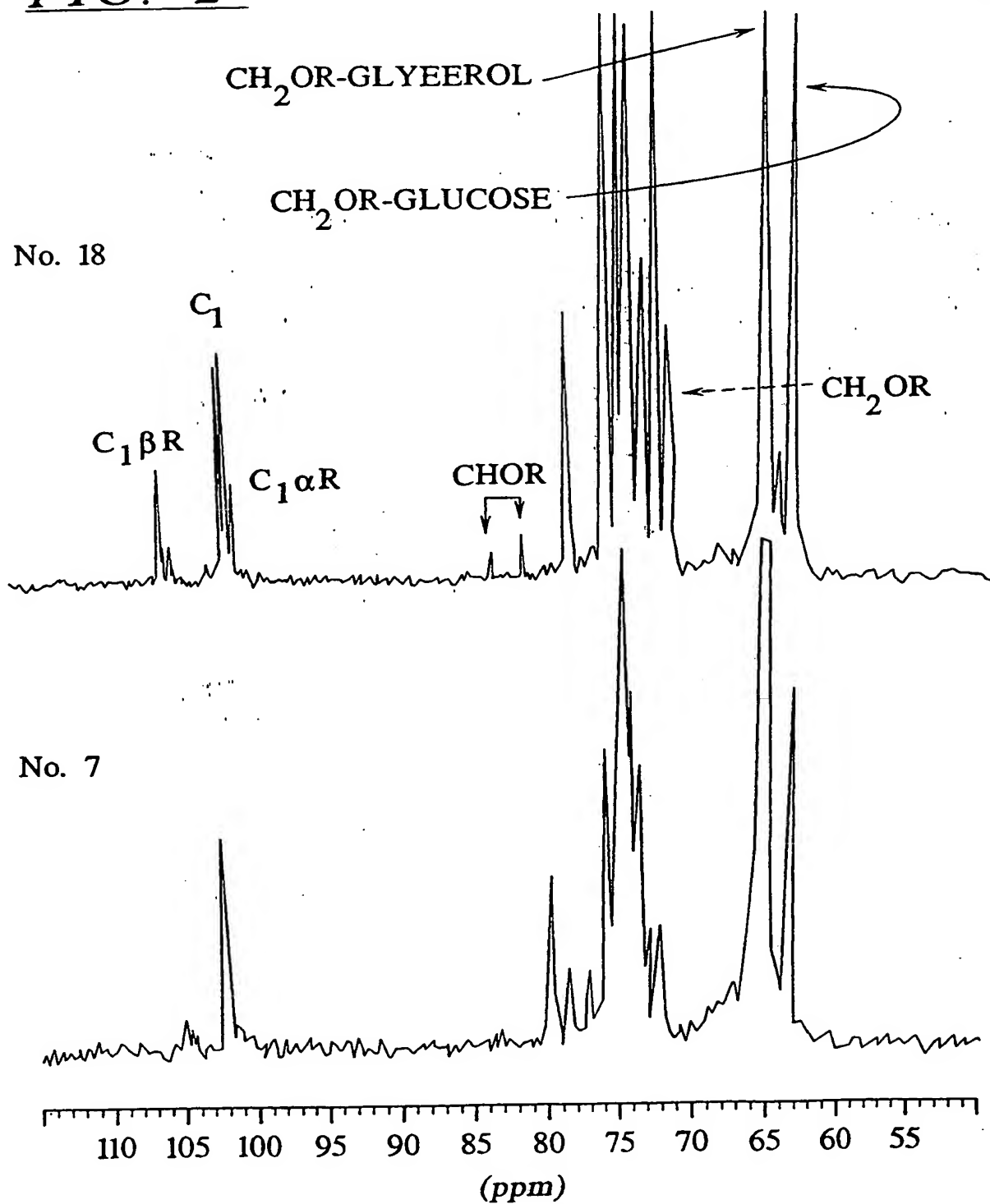


5

wherein R is selected from the group consisting of CH_3 , CH_3CH_2 and $(\text{CH}_2\text{OH})_2\text{CH}$.

FIG. 1

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FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/99/27456

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/715 A61P7/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 861 661 A (BAXTER) 2 September 1998 (1998-09-02) claim 1 page 4, line 3-6	1
A	EP 0 207 676 A (FISONS) 7 January 1987 (1987-01-07) claim 1 example 1	1

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

18 April 2000

Date of mailing of the international search report

26/04/2000

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